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Attorney's Docket No.: 17108-005001
(formerly, 18025-1014)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Partha S. Banerjee et al.	Art Unit	: 1617
Serial No.	: 09/887,496	Examiner	: Bahar, M.
Filed	: June 22, 2001	Conf. No.	: 7707
Title	: FORMOTEROL/STEROID BRONCHODILATING COMPOSITIONS AND METHODS OF USE THEREOF		

Mail Stop Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER OF APPEAL BRIEF

A Brief on Appeal, including an Appendix of Claims, relating to this application is enclosed (in triplicate). A Final Office Action was mailed on May 20, 2003, and a Notice of Appeal was filed on October 14, 2003. The required fees are computed below:

Appeal Brief	$ 330
Applicant hereby petitions under 37 C.F.R. §1.136 for a 4 month extension of time.	$1480
TOTAL FEE DUE	$1810

A check for $1,810.00 is attached. Please apply any charges not covered, or any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 4/12/04

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BRIEF ON APPEAL

(1) Real Party in Interest

The real party in interest herein is Dey, L.P., assignee of the entire interest in this application by virtue of an assignment from the inventors, recorded at Reel 012214, Frame 0107.

(2) Related Appeals and Interferences

There are no related applications on appeal or in interference.

(3) Status of Claims

Claims 1-64, 69-83, 87-89, 93 and 99-121 are pending and under appeal.

Claims 65-68, 84-86, 90-92 and 94-98 are cancelled.

(4) Status of Amendments

All amendments have been entered. No amendments are pending.

(5) Summary of Invention

The instant application provides pharmaceutical compositions containing (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid, where the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct

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administration to a subject in need thereof. The application further provides kits containing the pharmaceutical compositions and methods of use of the pharmaceutical compositions. The following table summarizes the page and line number in the specification upon which each appealed claim reads.

Claim	Specification Reference
1	Page 3, lines 25-31, and at page 5, line 17 to page 6, line 2
2	Page 4, lines 3-5
3	Page 4, lines 5-7
4	Page 4, lines 8-9
5	Page3, line31 to page 4, line 1
6	Page 4, line 1
7	Page 20, lines 29-31
8	Page 21, lines 3-20
9	Page 21, lines 20-21
10	Page 19, lines 5-6
11	Page 19, lines 5-30
12	Page 20, lines 1-2
13	Page 20, lines 3-4
14	Page 20, lines 3-5
15	Page 20, lines 5-6
16	Page 20, lines 19-21
17	Page 20, lines 19-21
18	Page 18, lines 12-13
19	Page 18, lines 16-17
20	Page 18, lines 16-17
21	Page 18, lines 19-20
22	Page 16, lines 20-23
23	Page 16, lines 25-27
24	Page 16, line 27
25	Page 17, line 8
26	Page 17, line 8
27	Page
28	Page 19, lines 5-6
29	Page 20, lines 1-2
30	Page 20, lines 3-4
31	Page 20, lines 3-5
32	Page 20, lines 5-6

Claim	Specification Reference
33	Page 20, lines 19-21
34	Page 20, lines 19-21
35	Page 18, lines 12-13
36	Page 18, lines 16-17
37	Page 18, lines 16-17
38	Page 18, lines 19-20
39	Page 16, lines 20-23
40	Page 16, lines 25-27
41	Page 16, line 27
42	Page 17, line 8
43	Page 17, line 8
44	Page 6, lines 13-14
45	Page 6, lines 13-14
46	Page 6, lines 13-14
47	Page 6, lines 13-14
48	Page 6, lines 13-14
49	Page 20, lines 1-2
50	Page 20, lines 5-6
51	Page 20, lines 19-21
52	Page 18, lines 19-20
53	Page 20, lines 1-2, Page 20, lines 5-6, Page 20, lines 19-21, Page 18, lines 19-20
54	Page 20, lines 1-2
55	Page 20, lines 5-6
56	Page 20, lines 19-21
57	Page 18, lines 19-20
58	Page 20, lines 1-2, Page 20, lines 5-6, Page 20, lines 19-21, Page 18, lines 19-20
59	Page 6, lines 13-14
60	Page 6, lines 13-14

Claim	Specification Reference
61	Page 19, line 30 to page 20, line 1
62	Page 19, line 30 to page 20, line 1
63	Page 6, lines 3-10
64	Page 6, lines 10-12
69	Page 17, line 12
70	Page 17, lines 18-20
71	Page 17, lines 24-25
72	Page 17, lines 26-28
73	Page 17, lines 11-12
74	Page 17, lines 11-12
75	Page 17, line 29
76	Page 17, line 29
77	Page 6, lines 13-14
78	Page 7, lines 13-16
79	Page 20, lines 1-2, Page 20, lines 5-6, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
80	Page 20, lines 1-2, Page 20, lines 5-6, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
81	Page 15, lines 28-29
82	Page 20, lines 1-2, Page 20, lines 5-6, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
83	Page 20, lines 1-2, Page 20, lines 5-6, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
87	Page 8, lines 5-12
88	Page 8, lines 5-12
89	Page 8, lines 5-12

Claim	Specification Reference
93	Page 29, lines 9-14, page 31, lines 15-30
99	Page 20, line 7
100	Page 20, line 7
101	Page 20, line 7
102	Page 20, line 7
103	Page 20, line 7
104	Page 20, lines 1-2, Page 20, lines 7, Page 20, lines 19-21, Page 18, lines 19-20
105	Page 20, line 7
106	Page 20, lines 1-2, Page 20, lines 7, Page 20, lines 19-21, Page 18, lines 19-20
107	Page 6, lines 13-14
108	Page 6, lines 13-14
109	Page 20, lines 1-2, Page 20, lines 7, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
110	Page 20, lines 1-2, Page 20, lines 7, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
111	Page 20, lines 1-2, Page 20, lines 7, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
112	Page 20, lines 1-2, Page 20, lines 7, Page 20, lines 19-21, Page 18, lines 19-20, Page 17, line 8
113	Page 29, line 13
114	Page 31, lines 3-8
115	Page 31, line 9

Claim	Specification Reference
116	Page 31, lines 10-11
117	Page 7, lines 7-9
118	Page 7, lines 12-13

Claim	Specification Reference
119	Page 7, lines 13-16
120	Page 31, lines 9-11
121	Page 31, lines 9-11

(6) Issues

(a) Whether claims 1-64, 69-83, 87-89, 99-112 and 117-119 are unpatentable under 35 U.S.C. § 103 over Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the Physician's Desk Reference (PDR) entry for fluticasone propionate.

(b) Whether claim 93 is unpatentable under 35 U.S.C. § 103 over Hochrainer *et al.* in view of Bartow *et al.* and PDR, as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119, and further in view of the PDR entries for albuterol, accolate and Zyflo.

(c) Whether claims 113-116, insofar as they read on ipratropium bromide, are unpatentable under 35 U.S.C. § 103 over Hochrainer *et al.* in view of Bartow *et al.* and PDR, as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119, and further in view of Hardman *et al.* (*Goodman Gilman's The Pharmacological Basis of Therapeutics*, 1996, pg 665).

(d) Whether claims 113-116, 120 and 121, insofar as they read on tiotropium bromide, are unpatentable under 35 U.S.C. § 103 over Hochrainer et al. in view of Bartow et al. and PDR, as applied to claims 1-64, 69-83, 87-89, 99-112 and 117-119, and further in view of Lieke *et al.* (*Novel Therapy of COPD, abstract, Jan. 2000*).

(7) Grouping of Claims

(a) Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103. The claims of this group do not stand or fall together. Claim 75 is directed to solution compositions. Claim 76 is directed to suspension compositions. The remaining claims, claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119, encompass both solution and suspension compositions.

(b) Claim 93 is rejected under 35 U.S.C. §103.

(c) Claims 113-116, insofar as they read on ipratropium bromide, are rejected under 35 U.S.C. §103.

(d) Claims 113-116, 120 and 121, insofar as they read on tiotropium bromide, are rejected under 35 U.S.C. §103.

(8) Argument

(a) REJECTION OF CLAIMS 1-64, 69-83, 87-89, 99-112 AND 117-119 UNDER 35 U.S.C. §103(a)

Claims 1-64, 69-83, 87-89, 99-112 and 117-119 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2)*:303-322) and the Physician's Desk Reference (PDR) entry for fluticasone propionate (FLOVENT®). It is alleged that the combination of these references results in the instantly claimed composition. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

[I]n order to establish a *prima facie* case of obviousness, there must be evidence, preferably a teaching, suggestion, incentive or inference from the cited art or in the form of generally available knowledge that one of ordinary skill would have been led to modify the relevant teaching to arrive at what is claimed. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

The prior art must provide a motivation whereby one of ordinary skill in the art would have been led to do that which the applicant has done. *Stratoflex Inc. v Aeroquip Corp.*, 713 F.2d 1530, 1535, 218 USPQ 871, 876 (Fed. Cir. 1983). In addition, the mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 USPQ 1783 (Fed. Cir. 1992).

In addition, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963).

A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed subject matter. See, *e.g.*, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See, *e.g.*, *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

The instant claims

Instant claim 1 is directed to a pharmaceutical composition, containing (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Claims 2-64, 69-74, 81-83, 87-89, 99-108, 111 and 112 are all dependent on claim 1 and therefore incorporate all of the limitations of claim 1.

Claim 75 is directed to the pharmaceutical composition of claim 1 that is a solution.

Claim 76 is directed to the pharmaceutical composition of claim 1 that is a suspension.

Claim 77 is directed to a nebulized suspension or solution, containing (i) formoterol or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid.

Claim 78 is directed to a kit, containing (a) an aqueous composition containing (i) formoterol or a derivative thereof, and (ii) a steroidal anti-inflammatory agent or a derivative thereof, formulated for single dosage administration; and (b) a nebulizer. Claims 79-80, 109 and 110 are dependent on claim 78 and therefore incorporate all of the limitations of claim 78.

Claim 117 is directed to a combination, containing a composition containing formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof; and a composition containing a bronchodilating steroid, or a derivative thereof.

Differences between the cited references and instant claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119

Hochrainer *et al.*

Hochrainer et al. teaches two compositions: 1) an "active substance concentrate;" and 2) a "pharmaceutical preparation."

"Active substance concentrate"

The "active substance concentrate" is not formulated at a concentration for direct administration to a subject in need thereof, as required by instant claim 1. The "active substance concentrate" is taught as a "highly concentrated" solution or suspension (*i.e.*, greater than 10 mg/mL, preferably 75 to 500 mg/mL) that is stable for a period of several months, possibly up to several years without any deterioration in the pharmaceutical quality (see, *e.g.*, column 1, lines 55-61; column 2, lines 4-7; and claim 1 of Hochrainer *et al.*). The "highly concentrated" "active substance concentrate" of the reference is not suitable for direct administration to a subject in need thereof, as required by instant claim 1. See, *e.g.*, column 2, lines 1-4:

> The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding solution or suspension to be used therapeutically for inhalation without being diluted.

See also, *e.g.*, column 1, lines 47-52:

> The active substance concentrate according to the invention may be converted, by diluting with a pharmacologically acceptable liquid which optionally contains pharmaceutical adjuvants and additives, into a pharmaceutical preparation (aerosol formulation) which is converted by means of a nebulizer into an inhalable aerosol.

See also, *e.g.*, column 4, lines 9-13:

> The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

Thus, the "active substance concentrate" of Hochrainer *et al.* is merely a means for the storage of highly concentrated compositions of formoterol, and is not formulated at a concentration for direct administration to a subject in need thereof, as required by claim 1.

"Pharmaceutical preparation"

Furthermore, Hochrainer *et al.* teaches that formoterol compositions formulated at a concentration for direct administration to a subject in need thereof *(i.e.,* "pharmaceutical preparations") are not stable, and therefore the reference teaches away from the claimed subject matter. See, *e.g.*, column 1, lines 30-35, where the reference teaches:

> In the past it has been found that liquid aerosol formulations of formoterol are not suitable for use in inhalers intended for ambulatory inhalation treatment since *formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time.* (emphasis added)

The Final Office Action states "[n]ote that nowhere does Hochrainer teach that its composition suitable for direct administration is unstable." The Final Office Action also states "[n]ote that [the] quotation [above] merely reports what was known in the art prior to the Hochrainer patent and cannot be construed to mean that the Hochrainer pharmaceutical composition itself will be unstable." Applicant respectfully disagrees with the Final Office Action's characterization of the teachings of Hochrainer *et al.*

The above-referenced quotation from Hochrainer *et al.* states more than the prior art knowledge. It states unequivocally that formoterol cannot be stored in a sufficiently stable manner in solution to guarantee the pharmaceutical quality of the formulation over lengthy periods of time. This is not stated merely in the context of prior compositions, but rather is stated as a property of formoterol itself. Therefore, Hochrainer *et al.* teaches away from the subject matter of instant claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119.

Example 3 of Hochrainer *et al.*

Moreover, Example 3 of Hochrainer *et al.* does teach that the "pharmaceutical preparation" of the reference is not stable during long term storage. Hochrainer *et al.* states in Example 3 (column 6, lines 55-59) that an aqueous solution of formoterol at pH 5.0 is not stable during long term storage (only 10% remaining after 3 months at 40 °C). This solution corresponds to the pharmaceutical preparations of Examples 1 and 2 of Hochrainer *et al.* Thus, Hochrainer *et al.* does teach in Example 3 that its "pharmaceutical preparation" is unstable during long term storage. Therefore, Hochrainer *et al.* teaches away from instant claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119.

A prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed subject matter. See, *e.g., W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). A *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See, *e.g., In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997).

Applicant respectfully submits that Hochrainer *et al.* materially teaches away from the subject matter of instant claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119. Hochrainer *et al.* teaches that aqueous "pharmaceutical preparation[s]" of formoterol formulated at a concentration for direct administration to a subject in need thereof are not stable during long term storage, as required by instant claim 1. Therefore, instant claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119 are not *prima facie* obvious over the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.*

Bartow *et al.* and the PDR entry for FLOVENT® do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Neither Bartow *et al.* nor the PDR teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Bartow *et al.* and the PDR do not teach or suggest modifying the "active substance concentrate" or the "pharmaceutical preparation" of Hochrainer *et al.* such that the composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof, as required by instant claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 1-64, 69-74, 77-83, 87-89, 99-112 and 117-119 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

Differences between the cited references and instant claim 75

As noted above, claim 75 is directed to pharmaceutical compositions of claim 1 that are solutions. In response to Applicant's arguments, an Advisory Action issued on October 8, 2003. The Advisory Action alleges that Example 3 of Hochrainer *et al.* merely teaches that formoterol aqueous solutions are not stable during long term storage, while formoterol aqueous suspensions are stable during long term storage. It is further alleged that the instant claims read on both suspensions and solutions, and therefore are allegedly obvious in view of the cited references. The Advisory Action states:

> Note that applicant argues that Example 3 is not stable during long term storage[.] Note that the recited part of the Hochrainer patent merely distinguishes between the stability of a formoterol aqueous solution and suspension at pH 5. Note that claims herein are drawn to a pharmaceutical composition in general (see claim1) encompassing both an aqeous [sic] solution and a suspension.

Thus, the Office has admitted that solution compositions of the instant claims, *i.e.*, of claim 75, are patentable over the cited references.

Applicant notes that the above is a mischaracterization of Applicant's arguments with respect to Example 3 of Hochrainer *et al.* and of the teachings of Example 3. Hochrainer *et al.* in Example 3 teaches that "active substance concentrate[s]" are stable, while "pharmaceutical preparation[s]" are not stable. The "active substance concentrate" of Hochariner *et al.* is not formulated at a concentration suitable for direct administration to a subject in need thereof, as required by instant claim 75. The "pharmaceutical preparation" of Hochrainer *et al.* is not stable during long term storage, as required by instant claim 75. As described in detail above, Bartow *et al.* and PDR do not cure the defects of Hochrainer *et al.* Therefore, as admitted by the Office, solution compositions of the instant claims are patentable over the cited references. Thus, instant claim 75, directed to solution compositions of claim 1, is patentable over the cited references.

Differences between the cited references and instant claim 76

As described in detail above, the Office admits the patentability of the instant claims if restricted to solutions. Applicant strongly believes that suspensions within the scope of the instant claims, *i.e.* claim 76, are also patentable over the teachings of the cited references. Applicant respectfully disagrees with the Office's interpretation of Example 3 of Hochrainer *et al.*

Example 3 of Hochrainer et al.

Example 3 of Hochrainer et al. recites as follows:

> In an aqueous solution with a pH of 5.0, formoterol breaks down to 10% at 40° C. within only 3 months. In a comparable suspension, no breakdown of any kind can be observed even after 6 months' storage at 40° C.

When read in the context of the Hochrainer *et al.* reference, *i.e.*, when the reference is read as a whole, this Example teaches more than a mere difference in stability between formoterol solutions and suspensions. The cited reference teaches that the "active substance concentrate" provided therein is stable during long term storage. See, *e.g.*, column 1, lines 55-61:

> The active substance concentrate according to the invention refers to solutions or suspensions in which formoterol is dissolved or suspended in highly concentrated form in a pharmacologically suitable fluid and which are characterized in that the active substance, formoterol, can be stored therein for a period from several months possibly up to several years without any deterioration in the pharmaceutical quality.

Therefore, the suspension of Example 3, which is stable for at least 6 months, must be an example of the "active substance concentrate" of Hochrainer *et al.*

The reference also teaches that the "active substance concentrate" is not formulated at a concentration for direct administration to a subject in need thereof, but must be diluted prior to administration. See, *e.g.*, column 4, lines 9-13:

> The active substance concentrate according to the invention is not usually suitable as such for direct medicinal use, particularly for inhalation. As already explained, use of the active substance concentrate comprises converting it into a pharmaceutical preparation (aerosol formulation).

See also, e.g., column 1, lines 55-57:

> The active substance concentrate according to the invention refers to...suspensions in which formoterol is...suspended in highly concentrated form...

See also, *e.g.*, column 2, lines 2-7:

> The term "highly concentrated" means a concentration of the active substance which is usually too high to enable the corresponding...suspension to be used therapeutically for inhalation without being diluted. According to the invention the formoterol concentration in the active substance concentrate is

between 10 mg/ml and 500 mg/ml. Preferably, the minimum concentration is at least 75 mg/ml.

The instantly-claimed compositions are formulated at a lower formoterol concentration (*e.g.*, a concentration for direct administration to a subject in need thereof), and do not require dilution prior to administration. The reference does not teach or suggest formoterol suspension formulations at this lower concentration that are stable during long term storage, as required by claim 76.

Therefore, Hochrainer *et al.* does not teach or suggest stable suspension formoterol compositions formulated at a concentration for direct administration to a subject in need thereof. Thus, Applicant respectfully submits that instant claim 76 is not *prima facie* obvious over the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.*

As noted above, Bartow *et al.* and the PDR entry for FLOVENT® do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Neither Bartow *et al.* nor the PDR teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Bartow *et al.* and the PDR do not teach or suggest modifying the "active substance concentrate" or the "pharmaceutical preparation" of Hochrainer *et al.* such that the composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof, as required by the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claim 76 is not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

(b) REJECTION OF CLAIM 93 UNDER 35 U.S.C. §103(a)

Claim 93 is rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.* (U.S. Patent No. 6,150,418) in view of Bartow *et al.* ((1998) *Drugs 55(2):*303-322) and the Physician's Desk Reference (PDR) entry for fluticasone

propionate (FLOVENT®), and further in view of the PDR entries for albuterol, accolate and Zyflo. It is alleged that the combination of these references results in the instantly-claimed composition. Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Claim 93

Instant claim 93 is directed to the pharmaceutical composition of claim 1, as described above, further containing one or more of (a) to (j) as follows: (a) a ß2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lypoxygenase inhibitor; or (j) an anti-IgE antibody.

Differences between the cited references and claim 93

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, the cited reference teaches stable formoterol aqueous suspension compositions that are not formulated at a concentration for direct administration to a subject in need thereof ("active substance concentrate"). Hochrainer *et al.* does not teach or suggest stable formoterol aqueous suspension compositions that are formulated at a concentration for direct administration to a subject in need thereof, as required by instant claim 93.

Furthermore, as noted in detail above, Hochrainer *et al.* does not teach or suggest stable formoterol aqueous solution compositions that are formulated at a concentration for direct administration to a subject in need thereof, as required by instant claim 93. Also, the Office admits that the instant claims, to the extent that they read on solution compositions, are patentable over the cited references. Therefore, instant claim 93 is not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.* and the PDR do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and the PDR entries for albuterol, accolate and Zyflo do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry

for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. The PDR entries for albuterol, accolate and Zyflo teach that albuterol, accolate and Zyflo are all known to be effective in treating asthma.

Instant claim 93 is directed to a pharmaceutical composition of claim 1, further containing one or more of (a)-(j). Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.* nor the PDR entries cited above teach or suggest modification of the "active substance concentrate" or the "pharmaceutical composition" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of instant claim 93. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claim 93 is not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.* and the PDR.

REJECTION OF CLAIMS 113-116, INSOFAR AS THEY READ ON IPRATROPIUM BROMIDE, UNDER 35 U.S.C. §103(a)

Claims 113-116, insofar as the read on ipratropium bromide, are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Hardman *et al.* (*Goodman Gilman's The Pharmacological Basis of Therapeutics*, 1996, page 665). Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

Differences between the cited references and the instant claims

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, the cited reference teaches stable formoterol aqueous suspension compositions that are not

formulated at a concentration for direct administration to a subject in need thereof ("active substance concentrate"). Hochrainer *et al.* does not teach or suggest stable formoterol aqueous suspension compositions that are formulated at a concentration for direct administration to a subject in need thereof, as required by instant claims 113-116.

Furthermore, as noted in detail above, Hochrainer *et al.* does not teach or suggest stable formoterol aqueous solution compositions that are formulated at a concentration for direct administration to a subject in need thereof, as required by instant claims 113-116. Also, the Office admits that the instant claims, to the extent that they read on solution compositions, are patentable over the cited references. Therefore, instant claims 113-116 are not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.*, the PDR and Hardman *et al.* do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and Hardman *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Hardman *et al.* teaches that ipratropium bromide is an anticholinergic agent useful in treating asthma.

Instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR nor Hardman *et al.* teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions of the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on ipratropium bromide) and 116 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Hardman *et al.*

REJECTION OF CLAIMS 113-116, INSOFAR AS THEY READ ON TIOTROPIUM BROMIDE, AND 120-121 UNDER 35 U.S.C. §103(a)

Claims 113-116, insofar as the read on tiotropium bromide, and 120-121 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over the teachings of Hochrainer *et al.*, Bartow *et al.* and the PDR, as above, and further in view of Leckie *et al.* (*Novel Therapy of COPD*, abstract, January 2000). Applicant respectfully requests reconsideration of this rejection in view of the following remarks.

Relevant Law

The relevant law is discussed above.

Instant claims 113-116 and 120-121

Instant claim 113 is directed to the pharmaceutical composition of claim 1, as described above, further comprising an anticholinergic agent. Claims 114-116, 120 and 121 are dependent on claim 113 and therefore incorporate all of the limitations of this claim.

Differences between the cited references and the instant claims

Hochrainer *et al.*

The teachings of Hochrainer *et al.* are discussed in detail above. As noted above, the cited reference teaches stable formoterol aqueous suspension compositions that are not formulated at a concentration for direct administration to a subject in need thereof ("active substance concentrate"). Hochrainer *et al.* does not teach or suggest stable formoterol aqueous suspension compositions that are formulated at a concentration for direct administration to a subject in need thereof, as required by instant claims 113-116 and 120-121.

Furthermore, as noted in detail above, Hochrainer *et al.* does not teach or suggest stable formoterol aqueous solution compositions that are formulated at a concentration for direct administration to a subject in need thereof, as required by instant claims 113-116 and 120-121. Also, the Office admits that the instant claims, to the extent that they read on solution compositions, are patentable over the cited references. Therefore, instant claims 113-116 and 120-121 are not obvious over the teachings of Hochrainer *et al.*

Bartow *et al.*, the PDR and Leckie *et al.* do not cure the defects of Hochrainer *et al.*

Bartow *et al.*, the PDR entry for FLOVENT® and Leckie *et al.* do not cure the defects of Hochrainer *et al.* Bartow *et al.* teaches the pharmacological properties and therapeutic efficacy of formoterol in the management of asthma. The PDR entry for FLOVENT® teaches pressurized, metered-dose aerosol units containing fluticasone propionate for oral inhalation. Leckie *et al.* teaches that tiotropium bromide is a known bronchiodilator employed in treating asthma.

Instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are directed to a pharmaceutical composition of claim 1, further containing an anticholinergic agent. Claim 1 recites that the pharmaceutical composition is stable during long term storage, the composition contains water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

Neither Bartow *et al.*, the PDR or Leckie *et al.* teach or suggest modification of the "active substance concentrate" or the "pharmaceutical preparation" taught in Hochrainer *et al.* to arrive at the pharmaceutical compositions used in the instant claims. Absent such teaching or suggestion, one of ordinary skill in the art would not have been motivated to do what applicant has done. Therefore, instant claims 113-115 (in so far as they read on tiotropium bromide) and 120-121 are not *prima facie* obvious over the teachings of Hochrainer *et al.* in view of Bartow *et al.*, the PDR and Leckie *et al.*

A check in the amount of $1810, including the brief fee of $330 and $1480 for a four-month extension of time, is enclosed. If a Petition for Extension of Time is needed, this paper is to be considered such Petition. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 4/12/04

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Appendix of Claims

1. A pharmaceutical composition, comprising (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof;

in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

2. The pharmaceutical composition of claim 1, wherein the composition has an estimated shelf-life of greater than 1 month usage time at 25 °C and greater than or equal to 1 year storage time at 5 °C.

3. The pharmaceutical composition of claim 2, wherein greater than about 80% of the initial formoterol is present after 1 month usage time at 25 °C and 1 year storage time at 5 °C.

4. The pharmaceutical composition of claim 1 that has been nebulized.

5. The pharmaceutical composition of claim 1, wherein the pharmacologically suitable fluid comprises a polar solvent.

6. The pharmaceutical composition of claim 5, wherein the polar solvent is a protic solvent.

7. The pharmaceutical composition of claim 6, further comprising a tonicity adjusting agent.

8. The pharmaceutical composition of claim 7, wherein the tonicity adjusting agent is ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, proplyene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium

sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine or zinc sulfate.

9. The pharmaceutical composition of claim 8, wherein the tonicity adjusting agent is sodium chloride.

10. The pharmaceutical composition of claim 1, wherein the pharmacologically suitable fluid comprises a buffer.

11. The pharmaceutical composition of claim 10, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris-(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonaic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonaic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane, HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropane-sulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxy-methyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

12. The pharmaceutical composition of claim 11, wherein the buffer is citrate buffer.

13. The pharmaceutical composition of claim 12, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

14. The pharmaceutical composition of claim 13, wherein the buffer concentration is from about 1 mM to about 20 mM.

15. The pharmaceutical composition of claim 14, wherein the buffer concentration is about 5 mM.

16. The pharmaceutical composition of claim 8, wherein the ionic strength of the composition is about 0 to about 0.4.

17. The pharmaceutical composition of claim 16, wherein the ionic strength of the composition is about 0.05 to about 0.16.

18. The pharmaceutical composition of claim 1, wherein the pH of the composition is about 2.0 to about 8.0.

19. The pharmaceutical composition of claim 18, wherein the pH of the composition is about 4.0 to about 6.0.

20. The pharmaceutical composition of claim 19, wherein the pH of the composition is about 4.5 to about 5.5.

21. The pharmaceutical composition of claim 20, wherein the pH of the composition is about 5.0.

22. The pharmaceutical composition of claim 1, wherein the formoterol free base concentration is about 5 μg/mL to about 2 mg/mL.

23. The pharmaceutical composition of claim 22, wherein the formoterol free base concentration is about 10 μg/mL to about 1 mg/mL.

24. The pharmaceutical composition of claim 23, wherein the formoterol free base concentration is about 50 μg/mL to about 200 μg/mL.

25. The pharmaceutical composition of claim 24, wherein the formoterol free base concentration is about 59 μg/mL.

26. The pharmaceutical composition of claim 24, wherein the formoterol free base concentration is about 118 μg/mL.

27. The pharmaceutical composition of claim 8, further comprising a buffer.

28. The pharmaceutical composition of claim 27, wherein the buffer is citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-

Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris-(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonaic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonaic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), tris(hydroxymethylaminomethane, HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropane-sulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxy-methyl)methyl-3-aminopropanesulfonic acid), or AMPD (2-amino-2-methyl-1,3-propanediol) buffer.

29. The pharmaceutical composition of claim 28, wherein the buffer is citrate buffer.

30. The pharmaceutical composition of claim 29, wherein the buffer concentration is from about 0.01 mM to about 150 mM.

31. The pharmaceutical composition of claim 30, wherein the buffer concentration is from about 1 mM to about 20 mM.

32. The pharmaceutical composition of claim 31, wherein the buffer concentration is about 5 mM.

33. The pharmaceutical composition of claim 27, wherein the ionic strength of the composition is about 0 to about 0.4.

34. The pharmaceutical composition of claim 33, wherein the ionic strength of the composition is about 0.05 to about 0.16.

35. The pharmaceutical composition of claim 27, wherein the pH of the composition is about 2.0 to about 8.0.

36. The pharmaceutical composition of claim 35, wherein the pH of the composition is about 4.0 to about 6.0.

37. The pharmaceutical composition of claim 36, wherein the pH of the composition is about 4.5 to about 5.5.

38. The pharmaceutical composition of claim 37, wherein the pH of the composition is about 5.0.

39. The pharmaceutical composition of claim 27, wherein the formoterol free base concentration is about 5 μg/mL to about 2 mg/mL.

40. The pharmaceutical composition of claim 39, wherein the formoterol free base concentration is about 10 μg/mL to about 1 mg/mL.

41. The pharmaceutical composition of claim 40, wherein the formoterol free base concentration is about 50 μg/mL to about 200 μg/mL.

42. The pharmaceutical composition of claim 41, wherein the formoterol free base concentration is about 59 μg/mL.

43. The pharmaceutical composition of claim 41, wherein the formoterol free base concentration is about 118 μg/mL.

44. The pharmaceutical composition of claim 25 that has been nebulized.

45. The pharmaceutical composition of claim 26 that has been nebulized.

46. The pharmaceutical composition of claim 42 that has been nebulized.

47. The pharmaceutical composition of claim 43 that has been nebulized.

48. The pharmaceutical composition of claim 27 that has been nebulized.

49. The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer.

50. The pharmaceutical composition of claim 42, wherein the buffer concentration is about 5 mM.

51. The pharmaceutical composition of claim 42, wherein the ionic strength of the composition is about 0.05 to about 0.16.

52. The pharmaceutical composition of claim 42, wherein the pH of the composition is about 5.0.

53. The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

54. The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer.

55. The pharmaceutical composition of claim 43, wherein the buffer concentration is about 5 mM.

56. The pharmaceutical composition of claim 43, wherein the ionic strength of the composition is about 0.05 to about 0.16.

57. The pharmaceutical composition of claim 43, wherein the pH of the composition is about 5.0.

58. The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer; the buffer concentration is about 5 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

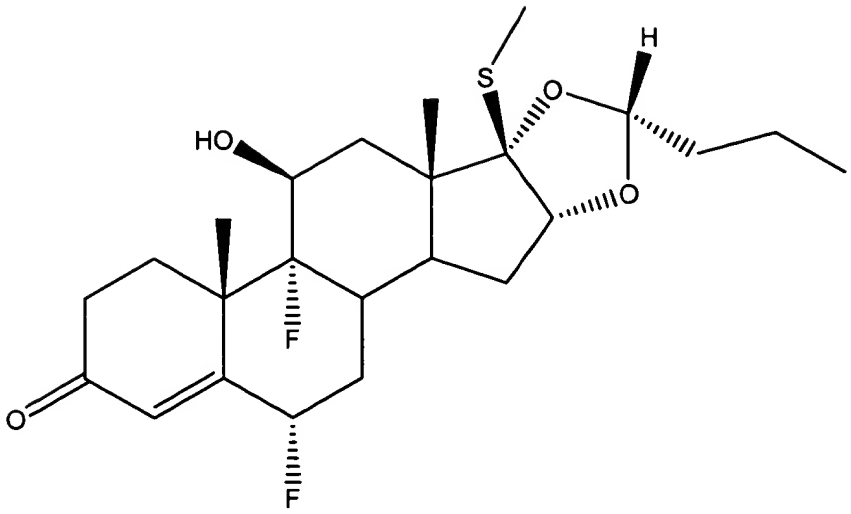
59. The pharmaceutical composition of claim 53 that has been nebulized.

60. The pharmaceutical composition of claim 58 that has been nebulized.

61. The pharmaceutical composition of claim 11, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

62. The pharmaceutical composition of claim 27, wherein the buffer comprises citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer.

63. The pharmaceutical composition of claim 1, wherein the steroidal anti-inflammatory agent is beclomethasone dipropionate, beclomethasone monopropionate, flunisolide, triamcinolone acetonide, dexamethasone, tipredane, ciclesonid, rofleponide, mometasone, mometasone furoate, RPR 106541 having the formula



fluticasone or fluticasone propionate, or budesonide, or a derivative thereof.

64. The pharmaceutical composition of claim 63, wherein the steroidal anti-inflammatory agent is budesonide or fluticasone propionate, or a derivative thereof.

69. The pharmaceutical composition of claim 64, wherein the steroidal anti-inflammatory agent is fluticasone propionate.

70. The pharmaceutical composition of claim 69, wherein the concentration of fluticasone propionate is about 5 μg/mL to about 2 mg/mL.

71. The pharmaceutical composition of claim 70, wherein the concentration of fluticasone propionate is about 75 μg/mL to about 1000 μg/mL.

72. The pharmaceutical composition of claim 71, wherein the concentration of fluticasone propionate is about 125 μg/mL or about 250 μg/mL.

73. The pharmaceutical composition of claim 53, wherein the steroidal anti-inflammatory agent is budesonide or fluticasone propionate.

74. The pharmaceutical composition of claim 58, wherein the steroidal anti-inflammatory agent is budesonide or fluticasone propionate.

75. The pharmaceutical composition of claim 1 that is a solution.

76. The pharmaceutical composition of claim 1 that is a suspension.

77. A nebulized suspension or solution, comprising (i) formoterol or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof; in a pharmacologically suitable fluid.

78. A kit, comprising:

(a) an aqueous composition comprising (i) formoterol or a derivative thereof, and (ii) a steroidal anti-inflammatory agent or a derivative thereof, formulated for single dosage administration; and

(b) a nebulizer.

79. The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

80. The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

81. A combination, comprising:

(a) the pharmaceutical composition of claim 1 formulated for single dosage administration; and

(b) a vial.

82. The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

83. The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 5 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

87. An article of manufacture, comprising packaging material, an aqueous composition comprising the composition of claim 1 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

88. An article of manufacture, comprising packaging material, the composition of claim 73 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

89. An article of manufacture, comprising packaging material, the composition of claim 74 formulated for single dosage administration, which is useful for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction, and a label that indicates that the composition is used for treatment, prevention or amelioration of one or more symptoms of diseases or disorders associated with undesired and/or uncontrolled bronchoconstriction.

93. The pharmaceutical composition of claim 1, further comprising one or more of (a) to (j) as follows: (a) a ß2-adrenoreceptor agonist; (b) a dopamine (D2) receptor agonist; (c) an IL-5 inhibitor; (d) an antisense modulator of IL-5; (e) a tryptase inhibitor; (f) a tachykinin receptor antagonist; (g) milrinone or milrinone lactate; (h) a leukotriene receptor antagonist; (i) a 5-lypoxygenase inhibitor; or (j) an anti-IgE antibody.

99. The pharmaceutical composition of claim 13, wherein the buffer concentration is from about 1 mM to about 50 mM.

100. The pharmaceutical composition of claim 99, wherein the buffer concentration is about 20 mM.

101. The pharmaceutical composition of claim 30, wherein the buffer concentration is from about 1 mM to about 50 mM.

102. The pharmaceutical composition of claim 101, wherein the buffer concentration is about 20 mM.

103. The pharmaceutical composition of claim 42, wherein the buffer concentration is about 20 mM.

104. The pharmaceutical composition of claim 42, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

105. The pharmaceutical composition of claim 43, wherein the buffer concentration is about 20 mM.

106. The pharmaceutical composition of claim 43, wherein the buffer is citrate buffer; the buffer concentration is about 20 mM; the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

107. The pharmaceutical composition of claim 104 that has been nebulized.

108. The pharmaceutical composition of claim 106 that has been nebulized.

109. The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

110. The kit of claim 78, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

111. The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 59 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

112. The combination of claim 81, wherein the aqueous composition comprises (a) formoterol free base at a concentration of about 118 μg/mL; (b) aqueous saline comprising sodium chloride; and (c) citrate buffer at a concentration of about 20 mM;

wherein the ionic strength of the composition is about 0.05 to about 0.16; and the pH of the composition is about 5.0.

113. The pharmaceutical composition of claim 1, further comprising an anticholinergic agent.

114. The pharmaceutical composition of claim 113, wherein the anticholinergic agent is ipratropium bromide, oxitropium bromide, atropine methyl nitrate, tiotropium bromide or glycopyrronium bromide.

115. The pharmaceutical composition of claim 114, wherein the anticholinergic agent is ipratropium bromide.

116. The pharmaceutical composition of claim 115, wherein the ipratropium bromide is present at a concentration of about 5 μg/mL to about 5 mg/mL.

117. A combination, comprising:

a composition comprising formoterol, or a derivative thereof, in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof; and

a composition comprising a bronchodilating steroid, or a derivative thereof.

118. The combination of claim 117, further comprising a nebulizer.

119. The combination of claim 118 that is packaged as a kit; optionally comprising instructions for use of the nebulizer; and optionally comprising instructions for mixing the compositions.

120. The pharmaceutical composition of claim 114, wherein the anticholinergic agent is tiotropium bromide.

121. The pharmaceutical composition of claim 115, wherein the tiotropium bromide is present at a concentration of about 5 μg/mL to about 5 mg/mL.